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10/601,242	06/20/2003	Phillip Dan Cook	ISIS-5213	6684
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WOODCOCK WASHBURN LLP			EPPS FORD, JANET L	
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/601,242	COOK ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Janet L. Epps-Ford	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

1) Responsive to communication(s) filed on 05 June 2007.  
 2a) This action is **FINAL**.                    2b) This action is non-final.  
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

4) Claim(s) 44 and 69-73 is/are pending in the application.  
 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.  
 5) Claim(s) \_\_\_\_\_ is/are allowed.  
 6) Claim(s) 44, and 69-73 is/are rejected.  
 7) Claim(s) \_\_\_\_\_ is/are objected to.  
 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

9) The specification is objected to by the Examiner.  
 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
     Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
     Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
 a) All    b) Some \* c) None of:  
 1. Certified copies of the priority documents have been received.  
 2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

1) <input type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413)
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	Paper No(s)/Mail Date. _____
3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____	5) <input type="checkbox"/> Notice of Informal Patent Application
	6) <input type="checkbox"/> Other: _____

## **DETAILED ACTION**

1. Claims 44, and 69-73 are pending for examination.
2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### ***Response to Arguments***

#### ***Claim Rejections - 35 USC § 103***

3. Claims 44, and 69-73 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Uhlmann et al., Cook et al., Secrist et al., and Sorge et al. for the reasons of record.
4. Applicant's arguments filed 6-05-07 have been fully considered but they are not persuasive. Applicants traverse the instant rejection on the grounds that absent evidence or reasoning of record as to why those of ordinary skill would have had such motivation to make, the modifications of the cited references. Moreover, Applicants assert that the Office's conclusion is not based on any particular findings that one skilled in the art would have selected the cited references for combination, rather, all that has been provided is the Office's bare assertion based upon the hindsight provided by Applicant's own disclosure.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

*Determining the scope and contents of the prior art:*

Ulhmann et al. describe the design of oligonucleotides comprising alpha-nucleosides, wherein the modified oligonucleotides proved to be astonishingly stable to nucleases (see page 556, section D.1.).

Cook et al. teach the following compound on page 163, line 33: 5'-Gaa-GTC-aCT-GgaaCG-3', wherein **a** is a 2'-deoxy- $\alpha$ -D-adenosine nucleoside. This compound comprises a region of  $\alpha$ -nucleosides and a region of  $\beta$ -deoxynucleosides synthesized by solid phase DNA synthesis from 5'-DMT-3'- $\beta$ -cyanoethyldiisopropyl-phosphoramidite protected deoxynucleosides. This compound is interpreted as meeting all the limitations of the claimed compound, to the extent that it comprises two regions, a region comprising  $\alpha$ -nucleosides, and a region comprising 2'-deoxyerythropentofuranosyl- $\beta$ -nucleosides.

Secrist et al. (1991) teach the synthesis and biological activity of 2'-deoxy-4'-thiopyrimidine nucleosides. Secrist et al. teach that several 4'-thioribonucleosides are resistant to bacterial cleavage and that 4'-thioinosine is resistant to cleavage by purine nucleoside phosphorylase, and suggests that the replacement of furanose ring oxygen may generally confer resistance to phosphorylases. Secrist et al. further suggest that incorporation of these compounds into DNA molecules may confer some useful biological activity (see page 2361, 2<sup>nd</sup> paragraph).

Sorge et al. (US Patent No. 5,354,656) teach the end modification of nucleic acid molecules with an alpha-thio-deoxynucleoside to protect the 3' end of the molecule from cleavage.

*Ascertaining the differences between the prior art and the claims at issue:*

The prior art describes polynucleotides containing, alpha-nucleoside or 4-thionucleosides, and further comprising a region of 2'-deoxynucleosides, and the difference between the claimed invention and the prior art is merely the number of consecutive 4'-thio or alpha-nucleosides, and 2'-deoxynucleosides in an oligonucleotide.

*Resolving the level of ordinary skill in the pertinent art:*

One of ordinary skilled artisan at the time of the instant invention seeking alternative modifications of antisense oligonucleotides for the purpose of increasing the half-life of the antisense oligonucleotide in cellular environments would have gathered all information available in the prior art regarding the effects of modifications on, for example, cleavage resistance to biological nucleases. The ordinary skilled artisan would have had within their purview the teachings of Ulmann et al., Cook et al., Secrist et al. and Sorge et al. One of ordinary skill in the art would have been motivated to employ the teachings of the prior art in the design of modified antisense oligonucleotides so long as the modifications are disclosed as increasing the biological properties of the modified antisense oligonucleotides, particularly in the absence of evidence to the contrary. As described above, the prior art discloses chimeric oligonucleotides comprising a combination of  $\alpha$ -nucleosides, and a region comprising 2'-deoxyerythropento-furanosyl- $\beta$ -nucleosides. Moreover, the prior art teaches that:

(a) modification of nucleic acid with alpha-thio-deoxynucleosides protects the 3' end of the nucleic acid molecule from cleavage; (b) incorporation of 2'-deoxy-4'-thiopyrimidine nucleosides into nucleic acid confer useful biological activities, including resistance to bacterial enzymatic cleavage; (c) and incorporation of alpha-nucleosides into oligonucleotides produced oligonucleotide that are astonishingly stable to nucleases. Therefore, the general benefits of alpha-nucleoside or 4'-thionucleoside modifications in oligonucleotides were known in the art at the time of filing of the instant application. Furthermore, absent evidence to the contrary, it would have been obvious to the ordinary skilled artisan to apply a known technique, namely using nucleoside modifications to increase the nuclease stability of an oligonucleotide. One of ordinary skill in the art would have recognized that applying this known technique would have yielded predictable results, particularly in improving the properties of an oligonucleotide as per the teachings of the prior art cited above, namely increasing the nuclease stability of oligonucleotides by incorporating 4'-thionucleosides or alpha-nucleosides as taught by the prior art.

*Considering objective evidence present in the application indicating obviousness or nonobviousness.*

Applicant's own specification at page 18, 1<sup>st</sup> paragraph teach also that α-nucleosides and 4'-thionucleosides function to impart nuclease stability to an oligonucleotide. Contrary to Applicant's assertions, the oligonucleotides modified by the teachings of the instant specification, to comprise α-nucleosides or 4'-thionucleosides are also expected to have the same properties as the oligonucleotides produced by the

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teachings of the prior art, specifically, increased nuclease resistance. Therefore, there is no evidence of unexpected properties (i.e. leading to a conclusion of non-obviousness) associated with the compounds modified according to the presently claimed invention.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

#### ***Claim Rejections - 35 USC § 112***

5. Claims 44 and 69-73 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. (New Matter).

6. Applicant's arguments filed 6-05-2007 have been fully considered but they are not persuasive. Applicants traversed the instant rejection on the grounds that because the specification as filed discloses an oligonucleotide comprising a 4 nucleotide long

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region of  $\alpha$ -nucleotides (see Example 2A), and an oligonucleotide comprising a region of four 4'-thionucleotides (Example 7) is sufficient to provide support for the instantly claimed invention that recite regions comprising a *plurality of consecutively* 4'thionucleosides or  $\alpha$ -nucleosides, *linked by charged 3'-5' phosphorous linkages*, and further comprising a region of at least 5 consecutive 2'-deoxy-erythro-pentofuranosyl  $\beta$ -nucleosides. Contrary to Applicant's assertions, the disclosure of oligonucleotides comprising four consecutive  $\alpha$ -nucleosides or 4'-thionucleosides is not sufficient to provide support for oligonucleotides comprising an region of undefined length comprising an undefined number of consecutively linked 4'thionucleosides or  $\alpha$ -nucleotides linked by charged 3'-5' phosphorous linkages.

It remains that Applicant's amendment is therefore considered new matter, since the scope of the claimed invention is not supported by the specification as filed.

### ***Conclusion***

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

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the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 10:00 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Janet L. Epps-Ford/  
Primary Examiner  
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JLE